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ABCA4-associated maculopathy suspected to be ocular toxoplasmosis

Maram E. A. Abdalla Elsayed[1,2†], Vincenzo Barone[3†] and Robert E. MacLaren[1,2*]

Abstract

Background Macular coloboma is a rare congenital anomaly that may mimic other retinal pathologies, including infectious disease and inherited retinal dystrophies. We report a young adult male with longstanding central vision loss and bilateral macular atrophic lesions resembling coloboma, ultimately found to harbour bi-allelic pathogenic variants in *ABCA4*.

Case presentation The patient underwent comprehensive ophthalmologic evaluation, including fundus imaging, optical coherence tomography (OCT), fundus autofluorescence (FAF), molecular genetic analysis, and segregation analysis. Macular dystrophy gene panel sequencing was performed. The patient was followed up for 20 years. OCT confirmed neurosensory retinal and choroidal loss at the fovea. Electro-diagnostics showed cone system dysfunction with preserved rod function. Genetic testing identified compound heterozygosity for two pathogenic ABCA4 variants (c.2160+1G>C and p.Thr1526Met), confirming ABCA4-associated retinopathy

Conclusion This case expands the phenotypic spectrum of ABCA4-related disease to include macular coloboma-like lesions. It also raises the possibility of coexisting retinal pathologies. Genetic testing should be considered in young patients with progressive visual loss and coloboma-like macular lesions, even in the absence of family history or evidence of intraocular inflammation.

Clinical trial number Not applicable.

Keywords *ABCA4*-associated retinopathy, Macular coloboma, Macular dystrophy, Inherited retinal diseases

Background

Macular colobomas are a rare ocular finding characterized by a sharply demarcated, oval or round macular lesion involving the neurosensory retina, retinal pigment epithelium (RPE), and choroid, often resulting in central visual loss [1]. Its pathogenesis is heterogeneous and includes congenital developmental anomalies, intrauterine infections, and inherited retinal dystrophies [2]. Although both congenital and acquired anomalies can produce bilateral macular lesions in children, distinguishing between these aetiologies is critical, given their differing implications for genetic counselling, clinical management, and prognosis [3].

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Macular coloboma encompasses a heterogeneous group of congenital and inherited maculopathies that can give rise to coloboma-like lesions. These include Best vitelliform macular dystrophy (BVMD), North Carolina macular dystrophy, *NMNAT1*-associated Leber congenital amaurosis, *ABCA4*-associated retinopathy, *PRPH2*-associated macular dystrophy, and torpedo maculopathy. Such entities often manifest with progressive macular atrophy that, particularly in advanced stages, may clinically mimic true macular coloboma [2, 4].

Additionally, intrauterine infections, notably *Toxoplasma gondii*, *rubella*, and *cytomegalovirus*, can lead to focal macular scars with coloboma-like morphology [2]. Macular colobomas have also been reported in association with various systemic syndromes, including *Down* syndrome, *Michaelis-Mentzel* syndrome, and others [5, 6].

As the most common cause of inherited retinal disease, with an estimated prevalence of 1 in 8,000 to 10,000 individuals, *ABCA4*-associated retinopathy may be considered a primary differential diagnosis in cases of early-onset macular dystrophy [7]. The *ABCA4* gene encodes an ATP-binding cassette (ABC) transporter localized to the outer segments of rod and cone photoreceptors, where it plays a critical role in the clearance of all-trans-retinal derivatives generated during the visual cycle [8]. There is vast allelic heterogeneity in *ABCA4*-related disease, with over 2,200 pathogenic variants reported to date. These are associated with phenotypes that include macular, cone, or cone–rod dystrophies and consist of small-scale insertions/deletions, splice-site, missense, nonsense, and copy-number variants [9].

Despite, imaging hallmarks such as foveal atrophy, perimacular flecks, outer retinal disruption on spectral-domain optical coherence tomography (SD-OCT), and characteristic patterns of hyper- and hypoautofluorescence on fundus autofluorescence (FAF) imaging, *ABCA4*-associated disease is notable for its phenotypic variability [7, 10]. As therapeutic clinical trials have already either commenced (e.g., pharmacological [clinicaltrials.gov identifier, NCT03735810, NCT03772665, NCT03033108, NCT02402660, NCT03364153], cellular [clinicaltrials.gov identifier, NCT03011541, NCT03772938], and gene therapy [clinicaltrials.gov identifier, NCT05417126]) or are planned, there is an urgent need to identify these patients.

In this report, we present a young adult male with a longstanding history of central visual impairment dating back to early childhood, who exhibited bilateral, excavated atrophic lesions involving both the neurosensory retina and underlying choroid. These findings initially raised clinical suspicion for ocular toxoplasmosis. However, the diagnosis was subsequently revised following electrophysiological and genetic testing, which suggested ABCA4-associated macular dystrophy.

The patient underwent full consultative ophthalmic examination at the Oxford Eye Hospital. Clinical data and genetic testing were performed as part of routine clinical care and data and results were collected retrospectively. Retinal imaging methods included pseudo-colour fundus Optos images (Optomap P200; Optos plc, Dunfermline, UK) and SD-OCT (Spectralis, Heidelberg Engineering, Inc., Heidelberg, Germany). Serological testing for IgG antibodies against *measles*, *rubella*, *cytomegalovirus* and *Toxoplasma gondii* were performed.

Full field electroretinography (ERG), pattern ERG (PERG), multifocal ERG (mfERG), and pattern-reversal visual evoked potentials (VEPs) were recorded according to the standards of the International Society for Clinical Electrophysiology of Vision (ISCEV) [11].

Informed consent for DNA blood sampling was taken from the patient, and the sample was sent to the Oxford Regional Genetics Laboratories (ORGL). A custom designed HaloPlex Target enrichment system (Agilent Technologies, Didcot, UK) was utilised to amplify the coding regions and intron/exon boundaries (+/− 10 bp) of the targeted genes and finally sequenced with Illumina MiSeq instrument (Illumina, San Diego, CA, USA) at the High-Throughput Genomics Group at the Wellcome Trust Centre for Human Genetics, Oxford. The utilised RetinalA_Macular panel includes the following genes: ABCA4, BEST1, C1QTNF5, CDH3, CNGB3, EFEMP1, ELOVL4, FSCN2, GUCA1A, GUCA1B, IMPG1, IMPG2, PROM1, PRPH2, RP1L1, RS1, and TIMP3. Detected variants were confirmed with Sanger sequencing. ORGL is accredited under the UKAS (United Kingdom Accreditation Service).

Case presentation

A 28-year-old Caucasian gentleman reported a progressive decline in central vision beginning in early childhood, with a notable deterioration between the ages of five and seven. At the age of seven, he underwent a full ophthalmologic evaluation, during which his best-corrected visual acuity (BCVA) measured 3/60 in the right eye and 4/60 in the left. His visual acuity had remained stable since. Intraocular pressure was within normal limits in both eyes, and no signs of intraocular inflammation were observed. Anterior segment examination was unremarkable, with no evidence of developmental anomalies. Retinal examination showed well-circumscribed macular excavation in both eyes, resembling macular colobomas. The lesion measured approximately one disc diameter in width and height in the right eye and was slightly smaller in the left. The foveal lesions were characterized by baring of the underlying sclera and were surrounded by a rim of pigmentary alteration. Additional superotemporal

and temporal areas of chorioretinal atrophy and pigmentation were noted in both eyes. All lesions have remained stable in size since the age of seven. Notably, no macular or peripheral drusen were present.

There was no relevant maternal drug exposure. There was no history of systemic disease, ocular trauma, or surgery. There was no known consanguinity, and no contact with animals or significant travel history was reported. Because of these findings, ocular toxoplasmosis was considered, based on the presence of a peripheral chorioretinal scar. Serological testing, performed at the same visit, revealed negative IgG antibodies against *cytomegalovirus*, *rubella*, *and Toxoplasma gondii.*

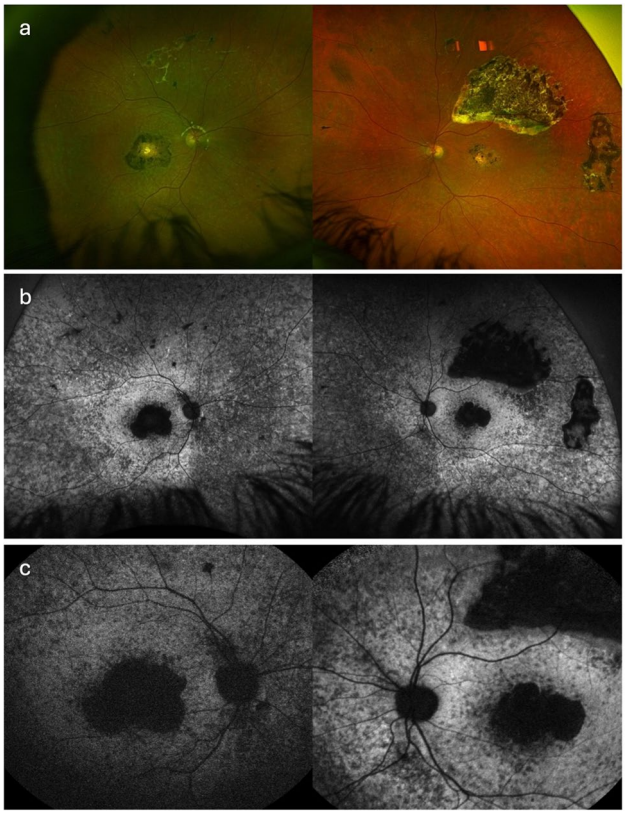

Fig. 1 Pseudo-colour fundus photographs (Optos), fundus autofluorescence (FAF), blue-light autofluorescence (BAF) showing bilateral macular coloboma-like lesions. (**a**) Pseudo-colour fundus image of the right eye (RE) showing foveal atrophy with surrounding pigmentation (on the left). Pseudo-colour fundus image of the left eye (LE) showing foveal atrophy with surrounding pigmentation, along with superotemporal and temporal areas of chorioretinal atrophy and pigmentation (on the right). (**b**) FAF image of the RE macula demonstrating a central hypoautofluorescent lesion surrounded by patchy hypoautofluorescent areas (on the left). FAF image of the LE macula show a similar central hypoautofluorescent lesion with additional superotemporal and temporal hypoautofluorescent areas (on the right). (**c**) BAF image of the RE showing central hypoautofluorescence with a surrounding mottled pattern of reduced signal (on the left). BAF image of the LE revealing a central hypoautofluorescent lesion and additional hypoautofluorescent areas in the superotemporal and temporal retina (on the right)

At subsequent visits within the same year, the patient underwent electrodiagnostic testing (ERG/VEP/PERG). Pattern-reversal VEPs showed delayed cortical responses in both eyes, with peak latencies ranging from 116 to 140 ms in the right eye and approximately 130 ms in the left eye. The corresponding amplitudes were approximately 6.0 µV and 8.0 µV, respectively. Flash VEPs were within normal limits. PERG revealed severely reduced responses bilaterally, with poorly formed waveforms and broadened major positivities measuring less than 1.0 µV in amplitude. Full-field ERGs, recorded using gold foil electrodes, demonstrated normal scotopic (rod-specific) responses with b-wave amplitudes of 180 µV in both eyes. The maximal combined response showed a-wave and b-wave amplitudes of 300 and 475 µV in the right eye, and 300 and 435 µV in the left eye, respectively. Photopic 30-Hz flicker ERGs revealed delayed implicit times and reduced amplitudes (50 µV in the right eye; 40 µV in the left). Single-flash photopic ERGs demonstrated reduced b-wave amplitudes (60 µV in the right eye; 50 µV in the left), along with a decreased b: a ratio. Additionally, photopic ON- and OFF-responses recorded in the right eye demonstrated an electronegative ON-response with relative preservation of the OFF-component, indicative of post-phototransduction involvement. These findings collectively supported a diagnosis of progressive cone dystrophy.

At the age of 12 years, autofluorescence imaging demonstrated a central dense hypoautofluorescent lesion in both eyes, surrounded by numerous scattered small, discrete hyperautofluorescent flecks distributed throughout the posterior pole and mid-periphery, with relative sparing of the peripapillary region. The left eye also showed additional dense peripheral zones of hypoautofluorescence located superior and temporal to the macula (Fig. 1). OCT revealed foveal excavation with complete loss of the neurosensory retina and choroid in the right eye, and retinal atrophy with partial choroidal loss in the left eye (Fig. 2).

Taken together, these findings were consistent with moderate generalized cone system dysfunction, post-phototransduction abnormalities, and significant bilateral macular impairment.

The patient was subsequently followed over time, and molecular genetic testing performed at one of his most recent visits, at the age of 27 years, identified compound heterozygosity for two ABCA4 variants: a pathogenic splice-site variant (c.2160 + 1G > C) and a missense variant classified as pathogenic/likely pathogenic (c.4577 C > T, p.Thr1526Met) according to American College of Medical Genetics and Genomics (ACMG) guidelines [12–17]. Segregation analysis confirmed that the patient's mother is heterozygous for the splice-site variant, while his father carries the missense variant.

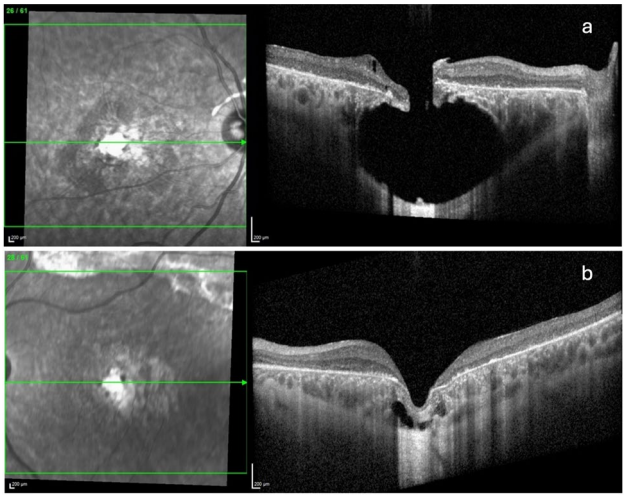

Fig. 2 Spectral-domain optical coherence tomography (OCT) scans of both eyes showing bilateral macular coloboma-like atrophic lesions. (**a**) OCT of the right eye demonstrating complete loss of the neurosensory retina and underlying choroid at the fovea, resulting in a sharply demarcated excavation. (**b**) OCT of the left eye showing marked atrophy of the neurosensory retina and partial loss of the underlying choroid at the foveal region

Discussion and conclusions

In this report, we describe an unusual presentation of bilateral macular coloboma-like lesions in a patient harboring bi-allelic pathogenic variants in the *ABCA4* gene.

The presence of peripheral chorioretinal scars initially raised the possibility of previous ocular toxoplasmosis; however, similar peripheral changes and subretinal fibrosis have been described in ABCA4-associated Stargardt disease and should also be considered in the differential diagnosis [10].

Given that ABCA4-related retinopathy may lead to secondary degeneration of the RPE, we hypothesize that early RPE cell loss in this case resulted in early choroidal atrophy, giving rise to the deep chorioretinal excavation referred to as macular coloboma. Similar patterns of chorioretinal atrophy have also been reported in other inherited retinal diseases, such as PRPH2-associated retinopathies [18].

In addition, while the overall phenotype may be compatible with congenital intrauterine chorioretinitis, the electrophysiological findings were instead indicative of cone dystrophy. Toxoplasma retinochoroiditis typically presents unilaterally and may recur, with an average of 2.7 episodes per patient [19]. Although lesions may appear well-demarcated, they usually lack the rounded or oval configuration typical of true macular colobomas. Serological testing for *Toxoplasma gondii* may support the diagnosis in appropriate clinical contexts; however, it should be noted that IgG assays may yield false-negative results, with reported rates ranging from 0% to 10.3% [20].

Although North Carolina macular dystrophy may resemble the current presentation, the majority of patients have stable vision and fundus findings throughout their lives. The ones who experienced decline in visual acuity do so because of the apparent evidence of choroidal neovascular membranes. In addition, being an autosomal dominant congenital developmental disorder, the condition is frequently associated with a positive family history [21]. In this patient, no macular or peripheral drusen were observed—findings most commonly associated with the MCDR1 locus, specifically involving non-coding variants upstream of the PRDM13 gene on chromosome 6q16. Additionally, the presence of widespread flecks on fundus autofluorescence made the diagnosis of North Carolina macular dystrophy unlikely [21].

NMNAT1-associated Leber congenital amaurosis typically presents in early infancy with severe vision loss, nystagmus, and progressive peripheral retinal degeneration. Pigmentary changes are commonly observed, but their distribution and intensity differ significantly from the fleck-like lesions seen in our patient. Additional features include arteriolar attenuation and optic atrophy [4]. In contrast, PRPH2-associated cone dystrophy tends to manifest later—usually between the second and fourth decades of life—and may progress to a macular lesion resembling geographic atrophy, with the presence of scattered and widespread hyperfluorescent flecks [22].

In cases of early-onset bilateral macular atrophy without evidence of intraocular inflammation or suspicion of congenital infection, especially when progressive visual loss is observed, an inherited retinal dystrophy should be strongly considered, even in the absence of a positive family history [23].

The genetic panel used in this case included a restricted number of genes, clearly limiting the genetic assessment and leaving open the possibility that additional variants—potentially coexisting or contributing to the pathology—were missed. Notably, PRDM13 and NMNAT1, which have been associated with North Carolina macular dystrophy and Leber congenital amaurosis respectively, were not included in the analysis. We acknowledge this as a limitation, as broader genetic testing could, in some cases, reveal additional variants of potential diagnostic relevance. However, in the present case, the clinical findings were not consistent with either North Carolina macular dystrophy or Leber congenital amaurosis, as previously discussed. Furthermore, the identification of two pathogenic ABCA4 variants provided a strong genotype–phenotype correlation. Nonetheless, in cases presenting with atypical features or inconclusive genetic results, extended testing strategies may be warranted to account for a wider spectrum of genetic conditions.

Abbreviations

ABC	ATP-binding cassette
BCVA	Best-corrected visual acuity
BVMD	Best vitelliform macular dystrophy
ERG	Electroretinography
FAF	Fundus autofluorescence
ISCEV	International Society for Clinical Electrophysiology of Vision
mfERG	Multifocal ERG
ORGL	Oxford Regional Genetics Laboratories
PERG	Pattern ERG
RPE	Retinal pigment epithelium
SD-OCT	SPECTRAL domain optical coherence tomography
UKAS	United Kingdom Accreditation Service
VEPs	Visual evoked potentials

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None.

Author contributions
M.E.A.A.E. and V.B. contributed equally to the conception, clinical evaluation, data interpretation, and manuscript drafting. R.E.M. supervised the project, provided critical revision of the manuscript, and approved the final version. All authors read and approved the final manuscript.

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Data availability
The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
All procedures were performed in accordance with the ethical standards of the institutional research committee and the Declaration of Helsinki. Written informed consent was obtained from the patient for participation in this study.

Consent for publication
Written informed consent was obtained from the patient for publication of clinical data and images.

Competing interests
The authors declare no competing interests.

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